Patents

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No.:

6,030,790

Patentees: **Knut Adermann et al.**

Serial No. **08/817,547**

Filed: **March 27, 1997**

For: **ANTIBODIES THAT BIND PEPTIDES FROM THE HPTH SEQUENCES**

Attn: Certificate of Correction Branch

CERTIFICATE OF CORRECTION OF OFFICE MISTAKE

Assistant of Commissioner of Patents
Certificate of Correction Branch
Washington, DC 20231

Sir:

The Patentees identified above, through the undersigned attorney of record, here request the Office to issue a Certificate of Correction for that patent. This request is made pursuant to 37 CFR 1.322 and is accompanied by Form PTO-1050 setting forth the text of the correction.

The error for which correction is sought is the omission from the printed patent of the last two paragraphs in page 9 and all of page 10 in the translated specification. A courtesy copy of the entire translated specification and claims, as submitted on March 27, 1997 with the request to enter the national phase, is attached for the convenience of the Office.

Accordingly, the Office is requested to issue a Certificate of Correction for this error.

Respectfully submitted,

Roger T. Frost
Reg. No. 22,176

KILPATRICK STOCKTON LLP
1100 Peachtree Street, Suite 2800
Atlanta, Georgia 30309-4530
(404) 815-6500
Docket: 07826-0007 (44816-236089)

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE

Patent No. 6,030,790
Patented: February 29, 2000

On petition requesting issuance of a certificate for correction of inventorship pursuant to 35 U.S.C. 256, it has been found that the above identified patent, through error and without deceptive intent, improperly sets forth the inventorship. Accordingly, it is hereby certified that the correct inventorship of this patent is:

Wolf-Georg Forssmann, Hannover, Germany; Knut Adermann, Hannover, Germany; Dieter Hock, Neckarbischofsheim, Germany; Markus Mägerlein, Obernburg, Germany

Signed and Sealed this Sixth Day of August 2002.

Yvonne Eyler, Ph. D.
Supervisory Patent Examiner
Art Unit 1646

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE

Patent No. 6,030,790
Patented: February 29, 2000

On petition requesting issuance of a certificate for correction of inventorship pursuant to 35 U.S.C. 256, it has been found that the above identified patent, through error and without deceptive intent, improperly sets forth the inventorship. Accordingly, it is hereby certified that the correct inventorship of this patent is:

Wolf-Georg Forssmann, Hannover, Germany; Knut Adermann, Hannover, Germany; Dieter Hock, Neckarbischofsheim, Germany; Markus Mägerlein, Obernburg, Germany

Signed and Sealed this Sixth Day of August 2002.

Yvonne Eyler, Ph. D.
Supervisory Patent Examiner
Art Unit 1646

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE

Patent No. 6,030,790
Patented: February 29, 2000

On petition requesting issuance of a certificate for correction of inventorship pursuant to 35 U.S.C. 256, it has been found that the above identified patent, through error and without deceptive intent, improperly sets forth the inventorship. Accordingly, it is hereby certified that the correct inventorship of this patent is:

Wolf-Georg Forssmann, Knut Adermann, Dieter Hock, and Markus Mägerlein.

Yvonne Eyler

Yvonne Eyler, Ph.D.
Supervisory Patent Examiner,
Art Unit 1646

3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No.:	)	
	)	
6,030,790	)	Art Unit: **1646**
	)	
Patentees: **Knut Adermann et al.**	)	Attn: **Supervisory Primary Examiner**
	)	
Serial No. **08/817,547**	)	
	)	
Filed: **March 27, 1997**	)	
	)	
For: **ANTIBODIES THAT BIND PEPTIDES FROM THE HPTH SEQUENCES**	)	

APPOINTMENT OF ASSOCIATE ATTORNEY

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please recognize James T. Carmichael, Reg. No. 45,306 of the firm of Lyon & Lyon LLP, 1701 Pennsylvania Avenue, N.W., Suite 1040, Washington, D.C., 20006, as Associate Attorney in the above-entitled application, and address all future communication to the firm.

Respectfully submitted,

By: Roger W. Frost
Reg. No. 22,176

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1100 Peachtree Street, Suite 2800
Atlanta, Georgia 30309-4530
(404) 815-6500
Docket: 07826-0007 (44816-236089)

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Patent
274/128

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of:	
Knut Adermann et al.	Group Art Unit: 1646
Patent No.: 6,030,790	Attention: Supervisory Primary Examiner
Filed: March 27, 1997	**HAND-CARRY TO EXAMINER**
For: ANTIBODIES THAT BIND PEPTIDES FROM THE HPTH SEQUENCES	

REQUEST FOR EXPEDITED HANDLING OF CERTIFICATE OF CORRECTION OF OFFICE MISTAKE

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants hereby petition for expedited handling of the accompanying petition for "Certificate of Correction of Office Mistake." The reason for expediting is that the above-identified patent is involved in litigation, as demonstrated by the pleadings filed herewith. These pleadings include:

- Complaint for Patent Infringement
- Answer and Counterclaim
- Scantibodies' Notice of Motion and Motion for Summary Judgment for Nonjoinder of Co-Inventor
- Scantibodies' Memorandum of Points and Authorities in Support of Motion for Summary Judgment
- Declaration of M. Andrew Woodmansee in Support of Scantibodies' Motion for Summary Judgment
- [Proposed] Order Granting Motion for Summary Judgment

Please charge or credit Deposit Account No. 12-2475 for any fees due, which are not covered by the enclosed check, as needed.

Respectfully submitted,

LYON & LYON LLP

Dated: 7/1/02

By: James T. Carmichael
Reg. No. 45,306

633 West Fifth Street, Suite 4700
Los Angeles, California 90071-2066
202-974-6018

Peptides from the hPTH(1-37) Sequence

The present invention relates to peptides from the sequence of hPTH(1-37), a diagnostic agent obtainable by immunization of animals using said peptides, antibodies or fragments thereof obtainable by immunization of animals using said peptides, and the use of said peptides in the preparation of an agent for diagnosing biologically active hPTH.

Human parathyroid hormone (hPTH), a linear polypeptide having 84 amino acids, plays an important role in the regulation of the calcium metabolism. The metabolism of this hormone gives rise to a large number of C-terminal fragments, the biological functions of which have not yet been elucidated. The hPTH(1-37) has been established as a circulating N-terminal fragment (EP-A 0 349 545). This fragment has the full biological activity of the entire hormone. However, upon loss of the first amino acid, serine, the activity significantly decreases and is lost completely without the first two amino acids, serine and valine.

Serum levels in the range of 10^{-12} mol/l are measured for the intact hormone hPTH(1-84) and for the N-terminal fragment. Immunological measuring procedures are employed to determine such low concentrations. Here, the most valid results are provided by measuring procedures according to the double antibody or sandwich principle (e.g., the two-site radioimmunometric assay, IRMA, or the sandwich enzyme-linked immuno sorbent assay, Sandwich ELISA). For hPTH(1-84), such assays are commercially available. For the measurement of hPTH(1-34), an assay according to the double antibody principle is not known.

Here, two antibodies are required. In order to avoid mutual steric hindrance, they must be capable of recognizing antigen epitopes located at a sufficient distance from each other. When immunizing using the intact antigen, a heterogeneous mixture of various antibodies is obtained, which first

must be subjected to an expensive purification in order to conduct a sandwich assay. According to theoretical calculations by B.A. Jameson and H. Wolf, The Antigenic Index: A Novel Algorithm for Predicting Antigenic Determinants, CABIOS 4, p. 181-186, 1988; it has been possible so far to detect a preferred sequence having immunogenic activity in the region of the amino acids 7-14 at the N-terminus. Immunization with N-terminal fragments according to established methods predominantly results in antibodies which, as has been described for hPTH(1-34) (J. Tampe, P. Brozio, H.E. Manneck, A. Mißbichler, E. Blind, K.B. Millers, H. Schmidt-Gayk, and F.P. Armbruster, Characterisation of Antibodies Against Human N-Terminal Parathyroid Hormone by Epitope Mapping; J. Immunoassay 13, p. 1-13, 1992), bind in the region of these amino acids. However, these antibodies are not capable of discriminating between biologically active and biologically inactive PTH(1-84) or fragments thereof lacking the first two amino acids serine and valine.

The technical problem which this invention is based upon is to provide peptides by means of which it is possible to eliminate the above-mentioned drawbacks in the diagnosis of biologically active hPTH.

Surprisingly, the technical problem described above is solved by means of peptides from the sequence of hPTH(1-37), which contain α-helical amino acid sequence regions and/or non-structured amino acid sequence regions, said peptides being capable of inducing antibodies when injected into animals. The peptides preferably contain the N-terminal α-helix in the region of the amino acids 5-9, a non-structured section of the amino acids 10-16, and/or a C-terminal α-helix in the region of the amino acid sequence 17-34 of hPTH(1-37). The following peptides of the invention are preferably used for immunizing:

hPTH 1-10

NH_2-Ser^1-Val^2-Ser^3-Glu^4-Ile^5-Gln^6-Leu^7-Met^8-His^9-Asn^{10}-OH (1)

hPTH 1-9

NH_2-Ser^1-Val^2-Ser^3-Glu^4-Ile^5-Gln^6-Leu^7-Met^8-His^9-OH (2)

hPTH 1-8

NH_2-Ser^1-Val^2-Ser^3-Glu^4-Ile^5-Gln^6-Leu^7-Met^8-OH (3)

hPTH 1-7

NH_2-Ser^1-Val^2-Ser^3-Glu^4-Ile^5-Gln^6-Leu^7-OH (4)

hPTH 1-6

NH_2-Ser^1-Val^2-Ser^3-Glu^4-Ile^5-Gln^6-OH (5)

hPTH 1-5

NH_2-Ser^1-Val^2-Ser^3-Glu^4-Ile^5-OH (6)

hPTH 9-18

NH_2-His^9-Asn^{10}-Leu^{11}-Gly^{12}-Lys^{13}-His^{14}-Leu^{15}-Asn^{16}-Ser^{17}-Met^{18}-OH (7)

hPTH 10-18

NH_2-Asn^{10}-Leu^{11}-Gly^{12}-Lys^{13}-His^{14}-Leu^{15}-Asn^{16}-Ser^{17}-Met^{18}-OH (8)

hPTH 11-18

NH_2-Leu^{11}-Gly^{12}-Lys^{13}-His^{14}-Leu^{15}-Asn^{16}-Ser^{17}-Met^{18}-OH (9)

hPTH 12-18

NH_2-Gly^{12}-Lys^{13}-His^{14}-Leu^{15}-Asn^{16}-Ser^{17}-Met^{18}-OH (10)

hPTH 13-18

NH_2-Lys^{13}-His^{14}-Leu^{15}-Asn^{16}-Ser^{17}-Met^{18}-OH (11)

hPTH 14-18

NH_2-His^{14}-Leu^{15}-Asn^{16}-Ser^{17}-Met^{18}-OH (12)

hPTH 9-17
NH_2-His^{9}-Asn^{10}-Leu^{11}-Gly^{12}-Lys^{13}-His^{14}-Leu^{15}-Asn^{16}-Ser^{17}-OH (13)

hPTH 9-16
NH_2-His^{9}-Asn^{10}-Leu^{11}-Gly^{12}-Lys^{13}-His^{14}-Leu^{15}-Asn^{16}-OH (14)

hPTH 9-15
NH_2-His^{9}-Asn^{10}-Leu^{11}-Gly^{12}-Lys^{13}-His^{14}-Leu^{15}-OH (15)

hPTH 9-14
NH_2-His^{9}-Asn^{10}-Leu^{11}-Gly^{12}-Lys^{13}-His^{14}-OH (16)

hPTH 9-13
NH_2-His^{9}-Asn^{10}-Leu^{11}-Gly^{12}-Lys^{13}-OH (17)

hPTH 24-37
NH_2-Leu^{24}-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-
Phe^{34}-Val^{35}-Ala^{36}-Leu^{37}-OH (18)

hPTH 25-37
NH_2-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-
Phe^{34}-Val^{35}-Ala^{36}-Leu^{37}-OH (19)

hPTH 26-37
NH_2-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-
Phe^{34}-Val^{35}-Ala^{36}-Leu^{37}-OH (20)

hPTH 27-37
NH_2-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-
Phe^{34}-Val^{35}-Ala^{36}-Leu^{37}-OH (21)

hPTH 28-37
NH_2-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-Phe^{34}-Val^{35}-Ala^{36}-Leu^{37}-OH (22)

hPTH 29-37
NH_2-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-Phe^{34}-Val^{35}-Ala^{36}-Leu^{37}-OH (23)

hPTH 30-37
NH_2-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-Phe^{34}-Val^{35}-Ala^{36}-Leu^{37}-OH (24)

hPTH 31-37
NH_2-Val^{31}-His^{32}-Asn^{33}-Phe^{34}-Val^{35}-Ala^{36}-Leu^{37}-OH (25)

hPTH 32-37
NH_2-His^{32}-Asn^{33}-Phe^{34}-Val^{35}-Ala^{36}-Leu^{37}-OH (26)

hPTH 33-37
NH_2-Asn^{33}-Phe^{34}-Val^{35}-Ala^{36}-Leu^{37}-OH (27)

hPTH 24-36
NH_2-Leu^{24}-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-Phe^{34}-Val^{35}-Ala^{36}-OH (28)

hPTH 24-35
NH_2-Leu^{24}-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-Phe^{34}-Val^{35}-OH (29)

hPTH 24-34
NH_2-Leu^{24}-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-Phe^{34}-OH (30)

hPTH 24-33
NH_2-Leu^{24}-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-OH (31)

hPTH 24-32
NH_2-Leu^{24}-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-OH (32)

hPTH 24-31
NH_2-Leu^{24}-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-OH (33)

hPTH 24-30
NH_2-Leu^{24}-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-OH (34)

hPTH 24-29

NH_2-Leu^{24}-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-OH (35)

hPTH 24-28

NH_2-Leu^{24}-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-OH (36)

The indicated sequences represent essential features of the secondary structure in their primary structure, as can be demonstrated by supporting NMR data. One precondition to this end was a determination of the PTH(1-37) secondary structure in physiological solution.

The above-mentioned regions of conspicuous structure have good immunogenic activity. Antibodies are formed, binding to the first amino acids of the N-terminus. Deficiency of only two amino acids gives rise to a substantial loss in affinity. Because these amino acids are indispensable for the biological activity to arise, it is possible by using the peptides of the invention to obtain antibodies recognizing only hPTH and fragments thereof which are biologically active.

Furthermore, antibodies can be produced which detect the mid-region 9-15, as well as antibodies giving C-terminal binding in the region of the amino acids 30-37. According to the invention, it is therefore possible to produce antibodies against hPTH(1-37) regions which, according to theoretical calculations, do not exhibit immunogenic activity within the entire molecule. In addition, these regions are separated from each other by such a far distance that no steric hindrance is present which would prevent simultaneous binding of two antibodies.

In preferred embodiments, the peptides may be modified at the N-terminal end, in the side-chain and/or at the C-terminal end, namely, taking the form of acetylation, amidation, phosphorylation and/or glycosylation products.

Eventually, the peptides of the invention may also be bound to carrier proteins such as hemocyanin, thyroglobulin, bovine serum albumin, ovalbumin, or mouse serum albumin etc.. Binding to the carrier proteins is preferably effected using carbodiimide or formaldehyde.

The peptides of the invention may be used in the preparation of a diagnostic agent. The diagnostic agent of the invention can be obtained using the per se known immunization of animals with at least one of the peptides according to the invention. Following immunization, an immunoglobulin fraction can be isolated from the immunized animals, which contains antibody fractions having an antibody titer against at least one of the peptides of the invention. The invention is also directed to the antibodies thus obtained. In addition to the complete antibodies consisting of F_{ab} and F_c, fragments thereof such as F_{ab} or fragments of the antibodies being idiotypes of peptide epitopes may also be used in an alternative embodiment.

The peptides according to the invention are suitable for preparing an agent for the diagnosis of biologically active hPTH(1-37).

Referring to the following examples, the invention will be described in more detail.

Example 1

Solid-Phase Synthesis of Peptides

The method of the invention for synthesizing the peptides is based on the peptide synthesis using a solid support. Each of the C-terminal amino acids is bound to the support material in the presence of dicyclohexylcarbodiimide and dimethylaminopyridine. Wang resin or similar resins are used as support material for the syntheses.

The following derivatives of L-amino acids are used in the synthesis of the sequence, starting from the peptidyl resin as specified: a) hPTH(1-10): Fmoc-Asn(Trt)-Wang resin, Fmoc-His(Trt)-OH, Fmoc-Met-OH, Fmoc-Leu-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Glu(OtBu)-OH, Fmoc-Ser(tBu)-OH, Fmoc-Val-OH, Boc-Ser(tBu)-OH; b) hPTH(9-18): Fmoc-Met-Wang resin, Fmoc-Ser(tBu)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Leu-OH, Fmoc-His(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Asn(Trt)-OH, Boc-His(Trt)-OH; c) hPTH(24-37): Fmoc-Leu-Wang resin, Fmoc-Ala-OH, Fmoc-Val-OH, Fmoc-Phe-OH, Fmoc-Asn(Trt)-OH, Fmoc-His(Trt)-OH, Fmoc-Val-OH, Fmoc-Asp(OtBu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Arg(Pmc)-OH, Fmoc-Leu-OH.

The synthesis may be carried out by <u>in situ</u> activation using 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) or derivatives thereof, or benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) or derivatives thereof in the presence of diisopropylethylamine or N-methylmorpholine and 1-hydroxybenzotriazole, using a four- to tenfold excess of Fmoc-L-amino acid during the coupling reactions in N,N-dimethylformamide, N,N-dimethylacetamide or N-methylpyrrolidone. Removal of the Fmoc groups is effected using 20% piperidine or 2% piperidine and 2% 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in N,N-dimethylformamide, N,N-dimethylacetamide or N-methylpyrrolidone. Following synthesis, the resins are washed with 2-propanol and dichloromethane and dried to constant weight in a high vacuum.

Removal from the support and deprotection are carried out by reacting the peptidyl resin with trifluoroacetic acid containing 5% scavenger, water, ethanediol, phenol or thioanisole for 30-90 minutes at room temperature, filtrating, washing with trifluoroacetic acid, and subsequently precipitating with tert-butyl methyl ether. The precipitate is lyophilized from aqueous solution.

Example 2

Purification and Analysis

The raw products are purified by chromatography on a C18 reversed phase column (10 µm, buffer A: 0.01 N HCl in water; buffer B: 20% isopropanol, 30% methanol, 50% water, 0.01 N HCl; gradient: 10-80% within 60 minutes; detection at 230 nm).

The purity of the products is determined using mass spectrometry and C18 reversed phase chromatography.

Example 3

Coupling to Carrier Protein

Used as carrier proteins are hemocyanin, thyroglobulin, bovine serum albumin, ovalbumin, or mouse serum albumin. Coupling is performed according to the carbodiimide method by way of the carboxyl groups of the peptides. The peptide is activated in aqueous solution by reaction with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride for 5 minutes. Coupling is effected by adding the activated peptide to an aqueous solution of the carrier. The molar ratio is 1 peptide on 50 amino acids of the carrier protein. The reaction takes 4 hours.

The reaction is stopped by adding sodium acetate with a final concentration of 100 mM. Incubation is allowed to proceed for one hour.

The protein-peptide conjugate is separated from the peptide by repeated dialysis against 100 mM phosphate buffer, pH 7.2.

Example 4

Synthesis of the Multiple Antigenic Peptides (MAP)

The triple lysine branching is achieved by binding Fmoc-L-lysine(Fmoc)-OH to C-terminal alanine bound to Wang resin using three coupling cycles. Cleavage with piperidine then results in eight free amino functions where the sequences of the human parathyroid hormone are synthesized according to the above description.

Example 5

Immunization

For the first immunization, 125 µg of carrier-peptide conjugate or MAP per kg body weight of the animal to be immunized is dissolved in 250 ml of water and emulsified with 250 µl of complete Freund adjuvant. The emulsion is applied subcutaneously in 10 portions at various positions on the back.

Boosting is carried out after 2-4 weeks in an analogous fashion, the only change being the substitution of the complete Freund adjuvant by the incomplete Freund adjuvant.

CLAIMS

1. Peptides from the sequence of hPTH(1-37), which contain α-helical amino acid sequence regions and/or non-structured amino acid sequence regions, said peptides being capable of inducing antibodies when injected into animals.

2. The peptides according to claim 1 from hPTH(1-37) having the sequence

hPTH 1-10
NH_2-Ser^1-Val^2-Ser^3-Glu^4-Ile^5-Gln^6-Leu^7-Met^8-His^9-Asn^{10}-OH (1)

hPTH 1-9
NH_2-Ser^1-Val^2-Ser^3-Glu^4-Ile^5-Gln^6-Leu^7-Met^8-His^9-OH (2)

hPTH 1-8
NH_2-Ser^1-Val^2-Ser^3-Glu^4-Ile^5-Gln^6-Leu^7-Met^8-OH (3)

hPTH 1-7
NH_2-Ser^1-Val^2-Ser^3-Glu^4-Ile^5-Gln^6-Leu^7-OH (4)

hPTH 1-6
NH_2-Ser^1-Val^2-Ser^3-Glu^4-Ile^5-Gln^6-OH (5)

hPTH 1-5
NH_2-Ser^1-Val^2-Ser^3-Glu^4-Ile^5-OH (6)

hPTH 9-18
NH_2-His^9-Asn^{10}-Leu^{11}-Gly^{12}-Lys^{13}-His^{14}-Leu^{15}-Asn^{16}-Ser^{17}-Met^{18}-OH (7)

hPTH 10-18
NH_2-Asn^{10}-Leu^{11}-Gly^{12}-Lys^{13}-His^{14}-Leu^{15}-Asn^{16}-Ser^{17}-Met^{18}-OH (8)

hPTH 11-18
NH_2-Leu^{11}-Gly^{12}-Lys^{13}-His^{14}-Leu^{15}-Asn^{16}-Ser^{17}-Met^{18}-OH (9)

hPTH 12-18
NH_2-Gly^{12}-Lys^{13}-His^{14}-Leu^{15}-Asn^{16}-Ser^{17}-Met^{18}-OH (10)

hPTH 13-18
NH_2-Lys^{13}-His^{14}-Leu^{15}-Asn^{16}-Ser^{17}-Met^{18}-OH (11)

hPTH 14-18
NH_2-His^{14}-Leu^{15}-Asn^{16}-Ser^{17}-Met^{18}-OH (12)

hPTH 9-17
NH_2-His^{9}-Asn^{10}-Leu^{11}-Gly^{12}-Lys^{13}-His^{14}-Leu^{15}-Asn^{16}-Ser^{17}-OH (13)

hPTH 9-16
NH_2-His^{9}-Asn^{10}-Leu^{11}-Gly^{12}-Lys^{13}-His^{14}-Leu^{15}-Asn^{16}-OH (14)

hPTH 9-15
NH_2-His^{9}-Asn^{10}-Leu^{11}-Gly^{12}-Lys^{13}-His^{14}-Leu^{15}-OH (15)

hPTH 9-14
NH_2-His^{9}-Asn^{10}-Leu^{11}-Gly^{12}-Lys^{13}-His^{14}-OH (16)

hPTH 9-13
NH_2-His^{9}-Asn^{10}-Leu^{11}-Gly^{12}-Lys^{13}-OH (17)

hPTH 24-37
NH_2-Leu^{24}-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-Phe^{34}-Val^{35}-Ala^{36}-Leu^{37}-OH (18)

hPTH 25-37
NH_2-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-Phe^{34}-Val^{35}-Ala^{36}-Leu^{37}-OH (19)

hPTH 26-37
NH_2-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-
Phe^{34}-Val^{35}-Ala^{36}-Leu^{37}-OH (20)

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NH_2-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-
Phe^{34}-Val^{35}-Ala^{36}-Leu^{37}-OH (21)

hPTH 28-37
NH_2-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-Phe^{34}-Val^{35}-Ala^{36}-
Leu^{37}-OH (22)

hPTH 29-37
NH_2-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-Phe^{34}-Val^{35}-Ala^{36}-Leu^{37}-OH (23)

hPTH 30-37
NH_2-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-Phe^{34}-Val^{35}-Ala^{36}-Leu^{37}-OH (24)

hPTH 31-37
NH_2-Val^{31}-His^{32}-Asn^{33}-Phe^{34}-Val^{35}-Ala^{36}-Leu^{37}-OH (25)

hPTH 32-37
NH_2-His^{32}-Asn^{33}-Phe^{34}-Val^{35}-Ala^{36}-Leu^{37}-OH (26)

hPTH 33-37
NH_2-Asn^{33}-Phe^{34}-Val^{35}-Ala^{36}-Leu^{37}-OH (27)

hPTH 24-36
NH_2-Leu^{24}-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-
Phe^{34}-Val^{35}-Ala^{36}-OH (28)

hPTH 24-35
NH_2-Leu^{24}-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-
Phe^{34}-Val^{35}-OH (29)

hPTH 24-34
NH_2-Leu^{24}-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-Phe^{34}-OH (30)

hPTH 24-33
NH_2-Leu^{24}-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-Asn^{33}-OH (31)

hPTH 24-32
NH_2-Leu^{24}-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-His^{32}-OH (32)

hPTH 24-31
NH_2-Leu^{24}-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-Val^{31}-OH (33)

hPTH 24-30
NH_2-Leu^{24}-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-Asp^{30}-OH (34)

hPTH 24-29
NH_2-Leu^{24}-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-Gln^{29}-OH (35)

hPTH 24-28
NH_2-Leu^{24}-Arg^{25}-Lys^{26}-Lys^{27}-Leu^{28}-OH (36)

3. The peptides according to claim 1 and/or 2, which are modified at the N-terminal end, in the side-chain and/or at the C-terminal end, taking the form of acetylation, amidation, phosphorylation and/or glycosylation products and/or are bound to carrier proteins such as hemocyanin, thyroglobulin, bovine serum albumin, ovalbumin, or mouse serum albumin.

4. A diagnostic agent which can be obtained using the per se known immunization of animals with at least one of the peptides according to at least one of claims 1 - 3, recovering fractions containing immunoglobulins from the immunized animals, and isolating fractions having an antibody titer against at least one of the

peptides according to at least one of claims 1 - 3, and which optionally contains additional adjuvants and/or vehicles.

5. Antibodies or fragments of antibodies, which can be obtained by immunizing animals with at least one of the peptides according to at least one of claims 1 - 3.

6. Use of the peptides according to at least one of claims 1 - 3 for producing an agent for the diagnosis of biologically active hPTH(1-37).

Abstract

The present invention is directed to peptides from the sequence of hPTH(1-37), which contain α-helical amino acid sequence regions and/or non-structured amino acid sequence regions, said peptides being capable of inducing antibodies when injected into animals. Furthermore, the invention is directed to a diagnostic agent and antibodies obtainable by immunizing animals using the peptides according to the invention.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No.:	)	
	)	
6,030,790	)	Art Unit: **1646**
	)	
Patentees: **Knut Adermann et al.**	)	Attn: **Supervisory Primary Examiner**
	)	
Serial No. **08/817,547**	)	
	)	
Filed: **March 27, 1997**	)	
	)	
For: **ANTIBODIES THAT BIND PEPTIDES FROM THE HPTH SEQUENCES**	)	

PETITION FOR CORRECTION OF INVENTORSHIP

Assistant of Commissioner of Patents
Washington , D.C. 20231

Attn: Supervisory Primary Examiner

Sir:

The above patentees, through the undersigned attorney of record, hereby petition to correct the inventorship named in that patent.

This petition is submitted pursuant to 37 C.F.R. 1.324 and is accompanied by the following documents:

(a) statement from the person being added as an inventor;

(b) a statement from the current inventors named on the patent;

(c) a statement from the assignee of record of the patent; and

(d) the fee set forth in section 1.20(b).

This patent was granted on an application for national-phase prosecution of International Application No. PCT/EP 95/03757. When entering the national phase, the three inventors currently named on the printed patent were identified as "inventors". However, a fourth person (Wolf-Georg Forssmann), was named in the international application as applicant and inventor ("Anmelder und Erfinder") but was omitted from the national-phase entry. This omission occurred through error and without any deceptive intention.

Accordingly, the Office is requested to issue a Certificate adding the following individual as an inventor in this patent:

Wolf-Georg Forssmann
Blücherstrasse 5
30175 Hannover, Germany

Upon granting of this petition, the corrected inventorship should read as follows:

Wolf-Georg Forssmann
Blücherstrasse 5
30175 Hannover, Germany

Knut Adermann
Schleidenstrasse 5
30177 Hannover, Germany

Dieter Hock
Weinbergstrasse 14
74924 Neckarsbischofsheim, Germany

Markus Mägerlein
Eichendorff Strasse 8
68167 Mannheim, Germany

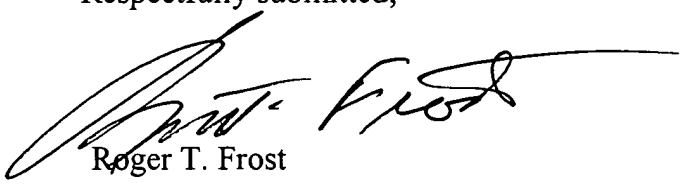
The enclosed statement of Wolf-Georg Forssmann states that the inventorship error occurred without any deceptive intention on his part.

The enclosed statement of the current named inventors shows that they agree to the change of inventorship.

The enclosed statement from the current assignee of all inventors, including Wolf-Georg Forssmann, shows that the assignee agrees to the change of inventorship.

The foregoing is submitted as full compliance with the requirements set forth in 37 C.F.R. 1.324. Accordingly, the Office is requested to issue a certificate adding Wolf-Georg Forssmann to the inventors named in this patent.

Respectfully submitted,



Roger T. Frost
Reg. No. 22,176

KILPATRICK STOCKTON LLP
1100 Peachtree Street, Suite 2800
Atlanta, Georgia 30309-4530
(404) 815-6500
Docket: 07826-0007 (44816-236089)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No.:	**6.030,790**		
Patentees:	**Knut Adermann et al.**	Art Unit:	**1646**
Serial No.:	**08/817,547**	Attn:	**Supervisory Primary Examiner**
Filed:	**March 27, 1997**		
For:	**ANTIBODIES THAT BIND PEPTIDES FROM THE hPTH SEQUENCES**		

STATEMENT OF MARKUS MÄGERLEIN

Assistant of Commissioner of Patents
Washington D.C. 20231

Attn. Supervisory Primary Examiner

Sir:

I, the undersigned, Markus Mägerlein, am an inventor currently named in the patent identified above. I agree to the requested change of inventorship, namely, adding Wolf-Georg Forssmann as an inventor named in that patent.

Date: June 12, 2002

Dr. Markus Mägerlein

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No.:	**6.030,790**		
Patentees:	**Knut Adermann et al.**	Art Unit:	**1646**
Serial No.:	**08/817,547**	Attn:	**Supervisory Primary Examiner**
Filed:	**March 27, 1997**		
For:	**ANTIBODIES THAT BIND PEPTIDES FROM THE hPTH SEQUENCES**		

STATEMENT OF DIETER HOCK

Assistant of Commissioner of Patents
Washington D.C. 20231

Attn. Supervisory Primary Examiner

Sir:

I, the undersigned, Dieter Hock, am an inventor currently named in the patent identified above. I agree to the requested change of inventorship, namely, adding Wolf-Georg Forssmann as an inventor named in that patent.

Date: June 10, 2002

Dr. Dieter Hock

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No.:	**6.030,790**		
Patentees:	**Knut Adermann et al.**	Art Unit:	**1646**
Serial No.:	**08/817,547**	Attn:	**Supervisory Primary Examiner**
Filed:	**March 27, 1997**		
For:	**ANTIBODIES THAT BIND PEPTIDES FROM THE hPTH SEQUENCES**		

STATEMENT OF ASSIGNEE

Assistant of Commissioner of Patents
Washington D.C. 20231

Attn. Supervisory Primary Examiner

Sir:

Pharis Biotec GmbH, a corporation under the laws of Germany and the owner by assignment of the patent identified above, agrees to add Wolf-Georg Forssmann to the inventors named in that patent.

Pharis Biotec GmbH

Date: June 10, 2002

Prof. Dr. Markus Meyer
Managing Director

Date: June 10, 2002

Dr. Michael Harder
Managing Director

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No.:	**6.030,790**		
Patentees:	**Knut Adermann et al.**	Art Unit:	**1646**
Serial No.:	**08/817,547**	Attn:	**Supervisory Primary Examiner**
Filed:	**March 27, 1997**		
For:	**ANTIBODIES THAT BIND PEPTIDES FROM THE hPTH SEQUENCES**		

STATEMENT OF KNUT ADERMANN

Assistant of Commissioner of Patents
Washington D.C. 20231

Attn. Supervisory Primary Examiner

Sir:

I, the undersigned, Knut Adermann, am an inventor currently named in the patent identified above. I agree to the requested change of inventorship, namely, adding Wolf-Georg Forssmann as an inventor named in that patent.

Date: June 10, 2002

Dr. Knut Adermann

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No.:	**6.030,790**		
Patentees:	**Knut Adermann et al.**	Art Unit:	**1646**
Serial No.:	**08/817,547**	Attn:	**Supervisory Primary Examiner**
Filed:	**March 27, 1997**		
For:	**ANTIBODIES THAT BIND PEPTIDES FROM THE hPTH SEQUENCES**		

STATEMENT OF WOLF-GEORG FORSSMANN

Assistant of Commissioner of Patents
Washington D.C. 20231

Attn. Supervisory Primary Examiner

Sir:

The failure to include the undersigned, Wolf-Georg Forssmann, as an inventor named in the patent identified above occurred without any deceptive intention on the part of the undersigned.

The undersigned acknowledges that on or about March 19, 1997, he signed a "Verified Statement (Declaration) by a Non-Inventor Supporting a Claim by Another for Small Entity Status". That statement was filed at the U.S. Patent and Trademark Office on or about March 27, 1997. My identification in that statement as a "non-inventor" was in error and occurred without any deceptive intention on my part.

Date: June 10, 2002

Prof. Dr. Wolf-Georg Forssmann

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Douglas E. Olson (State Bar Number 38649)
F.T. Alexandra Mahaney (State Bar Number 125984)
Moana L. McMullan (State Bar Number 199303)
BROBECK, PHLEGER & HARRISON LLP
12390 El Camino Real
San Diego, CA 92130-2081
Telephone: (858) 720-2500
Facsimile: (858) 720-3700

Attorneys for Plaintiff Nichols Institute Diagnostics Inc.

UNITED STATES DISTRICT COURT

FOR THE SOUTHERN DISTRICT OF CALIFORNIA

NICHOLS INSTITUTE DIAGNOSTICS, INC., a California Corporation,

Plaintiff,

v.

SCANTIBODIES CLINICAL LABORATORY, INC., a California Corporation; SCANTIBODIES LABORATORY, INC., a California Corporation; and DOES 1 through 10,

Defendants.

Case No.: '02 CV 0046 B (LAB)

COMPLAINT FOR PATENT INFRINGEMENT

DEMAND FOR JURY TRIAL

JURISDICTION AND VENUE

1. This lawsuit is an action for patent infringement. The Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338, and has jurisdiction over the parties.

2. Venue is proper in this district under 28 U.S.C. §§ 1391(b), 1391(c) and 1400(b). A substantial part of the events giving rise to the claim occurred in this district, Defendants' contacts with this district are sufficient to render them amenable to personal jurisdiction in this district, and Defendants have committed acts of infringement in this district. Defendants' contacts with this judicial district include the following: (1) Defendants' principal places of business are located in this district; (2) Defendants have purposefully directed the design and manufacture of infringing products which are in turn used, advertised, offered for sale and sold in this judicial district; and (3) Defendants have purposefully directed the use, advertisement, offer for sale and sale of infringing products in this judicial district. These contacts are related to, or gave rise to, the claims for patent infringement contained in this complaint.

PARTIES

3. Plaintiff NICHOLS INSTITUTE DIAGNOSTICS, INC. is a corporation organized under the laws of the State of California and has its principal place of business at 33051 Calle Aviador, San Juan Capistrano, California, 92675.

4. Defendant SCANTIBODIES CLINICAL LABORATORY, INC. is

a corporation organized and existing under the laws of the State of California and has its principal place of business at 9663 Abraham Way, Santee, CA, 92027.

5. Defendant SCANTIBODIES LABORATORY, INC. is a corporation organized and existing under the laws of the State of California and has its principal place of business at 9663 Abraham Way, Santee, CA, 92027.

FIRST CLAIM

(Infringement of U.S. Patent No. 6,030,790)

6. Plaintiff hereby incorporates by this reference paragraphs 1 through 5 inclusive.

7. U.S. Patent No. 6,030,790 ("the '790 Patent"), entitled "Antibodies That Bind Peptides From The HPTH Sequence (1-37)" was duly and lawfully issued on February 29, 2000. A true and correct copy of the '790 Patent is attached hereto as Exhibit 1.

8. Plaintiff is the exclusive licensee of the '790 Patent and has received all substantial rights under the '790 Patent including the right to prosecute infringement actions in the United States.

9. Defendants have been, and are currently, infringing the '790 Patent in violation of 35 U.S.C. § 271.

10. Upon information and belief, Defendants' acts of infringement will continue after service of this complaint.

11. Upon information and belief, Defendants' past and continued infringement is willful and deliberate, rendering this case appropriate for treble damages under 35 U.S.C. § 284 and making this an exceptional case under

35 U.S.C. § 285.

12. As a result of Defendants' infringement, Plaintiff has suffered and will suffer damages in the form of lost profits, or at a minimum, will be entitled to recover a reasonable royalty.

13. Unless Defendants are enjoined by this Court from continuing their infringement of the '790 Patent, Plaintiff will suffer additional irreparable damages and impairment of the value of its patent rights. Thus, Plaintiff is entitled to an injunction against further infringement.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff prays for judgment as follows:

A. That judgment be entered that Defendants are infringing the '790 Patent;

B. That Defendants, and their agents, servants, employees, successors and assignors, and all those acting under the authority of, or in privity or concert with them, and each of them, be preliminarily and permanently enjoined from directly or indirectly infringing the '790 Patent;

C. That judgment be entered for damages, together with prejudgment interest, to compensate Plaintiff for Defendants' infringement of the '790 Patent;

D. That judgment be entered for treble damages pursuant to 35 U.S.C. § 284;

E. That judgment be entered that this case is an exceptional case within the meaning of 35 U.S.C. § 285, and for an award of reasonable attorneys' fees to Plaintiff;

F. That judgment be entered for costs to be awarded to

Plaintiff; and

G. For such other and further relief as the Court may deem proper under the circumstances.

DEMAND FOR TRIAL BY JURY

Pursuant to the Federal Rules of Civil Procedure, Plaintiff respectfully demands a trial by jury.

Dated: January 8, 2002

Respectfully submitted,

BROBECK, PHLEGER & HARRISON, LLP

BY: _____
Douglas E. Olson
ATTORNEYS FOR PLAINTIFF

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,030,790

DATED : **March 27, 1997**

INVENTOR(S) : **Knut Andermann, et al.**

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 6, after line 56, insert the following text:

--The reaction is stopped by adding sodium acetate with a final concentration of 100mM. Incubation is allowed to proceed for one hour.

The protein-peptide conjugate is seperated from the peptide by repeated dialysis against 100 mM phosphate buffer, pH 7.2.

Example 4

Synthesis of the Multiple Antigenic Peptides (MAP)

The triple lysine branching is achieved by binding Fmoc-L-lysine (Fmoc) –OH to C-terminal alanine bound to Wang resin using three coupling cyles. Cleavage with piperidine then results in eight free amino functions where the sequences of the human parathyroid hormone are synthesized according to the above description.

Example 5

Immunization

For the first immunization, 125 mg of carrier-peptide conjugate or MAP per kg body weight of the animal to be immunized is dissolved in 250 ml of water and emulsified with 250 ml of complete Freund adjuvant. The emulsion is applied subcutaneously in 10 portions at various positions on the back.

Boosting is carried out after 2-4 weeks in an analogous fashion, the only change being the substitution of the complete Freund adjuvant by the incomplete Freund adjuvant.--

MAILING ADDRESS OF SENDER:

PATENT NO. 6,030,790

KILPATRICK STOCKTON LLP
1100 Peachtree Street, Suite 2800
Atlanta, Georgia 30309-4530

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FORM PTO 1050 (REV. 3-82)

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

NICHOLS INSTITUTE DIAGNOSTICS, INC., a California corporation,

Plaintiff,

v.

SCANTIBODIES CLINICAL LABORATORY, INC., a California corporation; and SCANTIBODIES LABORATORY, INC., a California corporation,

Defendants.

SCANTIBODIES CLINICAL LABORATORY, INC., a California corporation; and SCANTIBODIES LABORATORY, INC., a California corporation,

Counter-Claimants

v.

NICHOLS INSTITUTE DIAGNOSTICS, INC., a California corporation,

Counter-Defendants.

No. 02 CV 0046 B (LAB)

[PROPOSED] ORDER GRANTING MOTION FOR SUMMARY JUDGMENT PURSUANT TO 35 U.S.C. § 102(f) FOR NONJOINDER OF CO-INVENTOR

[Fed. R. Civ. P. 56]

This matter coming before the Court on Defendants' Motion for Summary Judgment for invalidity pursuant to 35 U.S.C. § 102(f), the Court, having considered the papers and arguments of counsel,

WHEREAS, Nichols Institute Diagnostics, Inc. ("Nichols") commenced this action for alleged infringement of U.S. Patent No. 6,030,790 (the "'790 patent");

WHEREAS, the '790 patent lists only three co-inventors on its face: Knut Adermann ("Adermann"), Dieter Hock ("Hock"), and Markus Mägerlein ("Mägerlein"). The '790 patent is the "national stage" of an earlier international patent application filed under the Patent Cooperation Treaty ("PCT"). As was appropriate under the PCT and the patent laws of the United States, the '790 patent claimed the filing date of the earlier PCT Application;

WHEREAS, the '790 patent does not name the same inventors as the PCT Application. The PCT Application identified Adermann, Hock, Mägerlein *and Wolf-Georg Forssmann* as inventors. The '790, however, does not include Forssmann; and

WHEREAS, the omission of Forssmann from the U.S. application for the '790 patent renders it invalid under 35 U.S.C. § 102(f),

NOW, THEREFORE, Defendants' Motion for summary Judgment is GRANTED. Nichols must now seek judicial correction of inventorship on notice and hearing of all concerned parties or have its patent declared invalid pursuant to section 102(f).

Hon. Rudi M. Brewster
U.S. District Court Judge